

Veterinary Transdermal Medications: A to Z

Transdermal medication delivery for veterinary patients (especially cats) is an answer to an age-old prayer from both veterinarians and pet owners. Delivering medication to cats noninvasively and without "kitty rodeos" and owner guilt is truly a landmark in veterinary pharmacotherapy. The transdermal delivery of medications has been well-documented in veterinary medicine for ivermectin, selamectin, fipronil, nitroglycerin, imidacloprid, and fentanyl. Many medications can be administered transdermally to veterinary patients (see Table 1) and there is a great desire to use that form of delivery for many others, but not every veterinary drug is suitable for transdermal use.

A recent US Food and Drug Administration (FDA) concept paper¹ on transdermal drug delivery suggests that the maximum amount of drug supplied by a transdermal patch could not exceed 1 mg/cm². Considering the surface area of the pinnae on any cat, it is unlikely that more than 25 mg of any drug could be absorbed transdermally. Before any drug is compounded in a transdermal dosage form, the veterinarian and the compounding pharmacist must carefully consider the pharmacologic characteristics of the drug with respect to the target species. They must also identify specific objective assessment parameters for determining the safety and efficacy of the treatment, as well as whether the risk of drug exposure to the client during administration precludes use of a transdermal dosage form. Transdermally delivered drugs bypass hepatic portal first-pass metabolism, and extrapolating oral doses to transdermal doses can result in toxicity.

To date there have been limited published studies of the pharmacokinetics, safety, or efficacy of compounded transdermal medications in veterinary patients. Until controlled studies provide evidence of safety and efficacy, the compounding pharmacist and veterinarian must use their best scientific judgment to predict whether a particular drug is suitable for transdermal

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delivery in a given patient. When transdermal agents are used, comprehensive data should be catalogued to determine clinical success or toxicity. For example, therapeutic blood concentrations used to quantify serum drug levels should be determined to indicate the disposition of drugs with established therapeutic concentrations (eg, phenobarbital, theophylline, aminoglycosides). Diagnostic information (eg, the blood glucose level, blood pressure, serum T4 levels, and results of urine cultures) should also be catalogued to indicate a response to transdermal therapy.

Ideally, transdermal dosage forms should be used only when traditional oral and injectable routes have not been effective. In this article, considerations for the transdermal use of several veterinary medications (including pharmacokinetic factors and assessment parameters for determining toxicity and efficacy) are presented. This information is meant only as a catalyst for thought; it in no way endorses the safety or efficacy of any of the listed drugs that are administered transdermally.

General Considerations

Bioavailability

Because it bypasses the gastrointestinal tract, transdermal dosing can approximate parenteral dosing. Harsh conditions in the gut can decrease the oral bioavailability of a drug, and hepatic portal extraction can also severely limit the amount of drug available for systemic circulation after oral administration. When assisting the veterinarian with the calculation of doses for transdermal drugs, the pharmacist should determine

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whether the target drug is available in an injectable and an oral form. If both forms of the drug are available, transdermal doses should initially approximate injectable doses. The dosage can then be adjusted according to the patient's response. If the target drug is not available in an injectable form, the oral bioavailability of the drug can be used to predict how much more drug is likely to be available for systemic circulation after transdermal administration. The fraction representing oral bioavailability should be considered when medications are administered transdermally. For example, if a drug has an oral bioavailability of only 60%, then no more than 60% of the oral dose should initially be applied transdermally. The dose will probably have to be increased to achieve the desired response, but it is always more desirable to titrate upward (toward efficacy) than downward (from toxicity).

Some drugs (eg, glipizide, amitriptyline) do not have a predictable efficacy by any route of administration. It is therefore wise to initially administer a course of therapy by traditional routes (oral or injectable) to determine whether a particular drug produces the desired response. Without clinical studies for efficacy and relative doses for transdermal drugs, therapeutic failure might be attributed to a transdermally administered drug in a patient that would have never responded to the drug by any route.

Metabolic Fate

The metabolic fate of a drug should be considered before it is compounded into a transdermal dosage form. Drugs hepatically metabolized will eventually cycle through the systemic circulation and reach the liver after transdermal administration. Drugs metabolized by cytochrome P450 enzymes in the gut wall may not be sufficiently metabolized after transdermal administration and may accumulate; this can result in toxicity. Prodrugs that are activated by gut-wall enzymes are not suitable for transdermal administration.

Effective Concentration at the Site of Action

The site of action of the drug must also be considered. For example, ursodiol is administered orally so that it will be significantly extracted via first-pass metabolism, during which it can exert its effect on bile in the liver. Administering ursodiol transdermally would prevent its reaching a significant concentration in bile.

As previously mentioned, drugs requiring dosages of more than 25 mg are not likely to be completely absorbed when administered transdermally. Because most veterinary antibiotics are administered at doses greater than 25 mg, transdermal delivery may result in subtherapeutic concentrations and may increase the risk of bacterial resistance. The tendency of cat skin to depot and slowly release drugs could contribute to a lower C_{max} , which would result in a subtherapeutic minimum inhibitory concentration at the site of infection. Doxycycline is an antibiotic that should not be compounded transdermally. Doxycycline has been shown to ulcerate when lodged in a cat's esophagus, and the development of bacterial resistance to that drug is a possibility. Rubbing a highly concentrated

doxycycline gel on the paper-thin ears of a cat twice daily would probably result in severe ulceration of the pinnae. Doxycycline is also a potent photosensitizer. If it is applied transdermally to an outdoor cat, exposure to sunlight would cause lesions on the pinnae. For those and similar reasons, antibiotics are usually not administered transdermally.

Some classes of drugs must be administered orally to exert their effects locally. Aluminum hydroxide gel works in the gut by binding phosphate to reduce hyperphosphatemia in patients with renal failure. Transdermally administered aluminum hydroxide would fail to bind phosphate in the gut and would thus prevent phosphate absorption. Anthelmintic drugs also may exert their effect against gut parasites locally. Epsiprantel is not orally absorbed at all; high concentrations in the gut lumen produce the desired effect on intestinal tapeworms.

Drugs with a Narrow Therapeutic Index

Drugs with a narrow therapeutic index should not be administered transdermally. Cyclosporine, digoxin, and warfarin should never be administered transdermally and could be fatal if dosed incorrectly.

Diagnostic Agents

Diagnostic agents are administered either to evoke or to fail to elicit a very specific physiologic response from a target organ. Doses of drugs such as liothyronine, corticotropin, dexamethasone, and glucagon have been carefully calibrated to produce a certain response in a healthy animal. If the anticipated response does not occur, disease may be present. Variation in the expected response indicates the degree of disease. Delivery of an insufficient amount of drug or delivery of a drug at a different rate after transdermal administration will result in inaccurate diagnostic test results and may falsely indicate disease in a healthy animal.

Glucocorticoids

The long-term administration of topical corticosteroids eventually causes epidermal atrophy and causes the loss of skin integrity. The concentrations of corticosteroids (eg, prednisolone 5 mg/0.1 mL or 50 mg/mL) in transdermal gels are far higher than those in topical corticosteroid ointments and creams. Anecdotal reports indicate atrophy of the epidermis and cartilage in the ears of cats after only a few weeks of transdermal prednisolone therapy. Whether the "floppy ears" of cats with those sequelae will return to normal is unknown, but the long-term use of transdermal corticosteroids should usually be avoided.

Risks to the Caregiver

Any drug that is potentially toxic to the human administering the drug should not be prescribed for topical application. Chemotherapeutic agents, medications with a narrow therapeutic index, and chloramphenicol should never be administered transdermally because they may be toxic to the caregiver. The general health of the caregiver should also be considered before transdermal drugs are prescribed. For example, a hypothyroid female caregiver probably should not administer

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Table 1. Veterinary Drugs Considered for Transdermal Therapy.

Drug	Cats		Max. Recommended Starting TD Dose*	Target for Efficacy	Monitoring Symptoms of Toxicity
	Oral Dose	Injectable Dose			
Aminophylline					
100% Bioavailability for non-SR orals; injectable doses equal to oral doses; TD forms used successfully in human neonates	4 mg/kg q 8 to 12 hr	4 mg/kg q 8 to 12 hr	4 mg/kg q 8 to 12 hr	Serum theophylline blood level in therapeutic range (those values are not firmly established for veterinary patients, but the human range is 10 to 20 µg/mL); evidence of controlled asthma	Tachycardia, arrhythmia, seizure, hyperthermia
Amitriptyline					
48% Oral bioavailability (humans); extensive first-pass hepatic extraction; accumulation after multiple doses; active metabolites must be conjugated with glucuronic acid to inactivate (cats cannot do that)	5 to 10 mg/cat q 24 hr	NP	1.25 mg/cat q 24 hr; behaviorists who have used TD amitriptyline in cats advise careful monitoring to avoid accumulation	Cessation of undesirable behavior; cessation of cystitis; onset of action as early as 3 to 5 days after initiation of therapy	Dry mouth, gastric distress, constipation, ataxia, tachycardia, weakness, sedation, urinary retention
Amlodipine					
Oral bioavailability 75% in humans, undetermined in cats; slowly but extensively metabolized to inactive compounds in the liver	0.625 mg/cat q 24 hr	NP	0.625 mg/cat q 24 hr	Reduction in blood pressure	Headache is reported most commonly in humans, although it may be difficult to recognize in veterinary patients; hypotension
Amoxicillin clavulanate					
NR because doses > 50 mg are required and possibility of induction of bacterial resistance	62.5 mg/cat q 24 hr	NP	NR	NR	ROB
Atenolol					
50% Oral bioavailability; minimal (< 50%) metabolism	6.25 mg/cat q 24 hr	NP	3.25 mg/cat q 24 hr	Reduction in pulse to 140 to 200 beats per minute	Hypotension, bradycardia, bronchospasm, cardiac failure, hypoglycemia
Azithromycin					
NR because doses > 50 mg are required and possibility of induction of bacterial resistance	7 to 15 mg/kg q 12 hr for 5 to 7 days, then every 5 days	NP	NR	Eradication of bacterial infection	Head tilt (otic toxicity), elevated hepatic enzymes
Buprenorphine					
Injectable form available; high degree of first-pass extraction with gut wall and liver metabolism, conjugation with glucuronide	0.01 to 0.03 mg/kg up to q 8 hr	0.005 to 0.015 mg/kg IM, IV	0.01 mg/kg q 8 hr	Apparent analgesia, animal benefiting from pain management	Respiratory depression
Buspirone					
NR until further studies available; extensive first-pass extraction (95% of oral dose removed by hepatic extraction)	2.5 mg/cat q 12 hr	NP	NR	Cessation of undesirable behavior or phobia	Sedation, anorexia, nausea, tachycardia
Butorphanol					
Extensive first-pass extraction (84% of oral dose removed by hepatic extraction)	1 mg/cat PO q 12 hr	0.4 mg/kg SQ q 6 hr	0.4 mg/kg q 6 hr	Apparent analgesia, animal benefiting from pain management	Oversedation, respiratory depression

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Drug	Cats		Max. Recommended Starting TD Dose*	Target for Efficacy	Monitoring Symptoms of Toxicity
	Oral Dose	Injectable Dose			
Carboplatin					
NR. Cytotoxic agent; tissue necrosis occurs at concentrations > 0.5 mg/mL	NR	NR	NR	NR	NR
Chloramphenicol					
NR. Highly toxic to humans, bacterial resistance; large doses preclude transdermal dosing	NR	NR	NR	NR	NR
Cisapride					
Oral bioavailability 35% to 40%; can be problematic to caregiver who may be taking drugs such as antihistamines and benzimidazole antibiotics, which may interact with cisapride	5 mg/cat q 8 to 12 hr	NP	2.5 mg/cat q 12 hr	Resolution of ileus, evidence of colonic motility with no constipation or obstruction	Diarrhea, abdominal pain and cramping, arrhythmia from drug interactions
Clomipramine					
Substantial first-pass hepatic extraction; oral bioavailability 50%; may accumulate in cats, which are very sensitive to tricyclic antidepressants	2.5 mg/cat q 24 hr	NP	1.25 mg/cat q 24 hr	Cessation of undesirable behavior	Excessive sedation, dry mouth, urinary retention
Cyclophosphamide					
NR. Cytotoxic agent	NR	NR	NR	NR	NR
Cyproheptadine					
Good oral bioavailability; extensive hepatic metabolism and conjugation with glucuronide; metabolites excreted in urine; accumulates in renal failure	2 mg/cat q 12 hr	NP	2 mg/cat q 12 hr; monitor for accumulation	Stimulation of appetite, relief of pruritus, cessation of undesirable behavior	Excessive sedation, dry mouth, urinary retention
Digoxin					
NR. Narrow therapeutic index; cats are very sensitive to digoxin; potential exposure by caregiver	0.007 to 0.015 mg/kg q 24 to 48 hr. Do not use in hypertrophic cardiomyopathy in cats	NP	NR	Achievement of therapeutic serum levels: serum 0.9-2.0 ng/mL for cats	Cats very sensitive. Bradycardia, worsening of arrhythmia, levels > 2.0 ng/mL
Diltiazem					
10% Transdermal bioavailability in cats (compared with IV administration); extensive first-pass hepatic extraction (50% to 80% oral bioavailability in cats)	7.5 mg/cat (non-SR) q 8 hr	0.25 mg/kg IV bolus up to 0.75 mg/kg	7.5 mg/cat q 12 hr to q 24 hr	Reduction in pulse rate to 140 to 200	Bradycardia, vomiting, heart block
Doxycycline					
Irritating to gastric and esophageal mucosa of cats; rubbing this chemical into ears is NR; also a potent photosensitizer; application to ears that might be exposed to sunlight is NR; bacterial or rickettsial resistance to this drug from subtherapeutic concentrations leaves few alternatives for treating tick-borne disease	5 mg/kg q 12 hr	5 mg/kg IV q 24 hr	NR	NR	NR

*Until scientific studies or clinical experience indicates otherwise, the doses in Table 1 are suggested as the maximum starting dose for the drugs listed. Those suggested doses do not guarantee the safety or efficacy of the medication in any patient. Future scientific studies may completely invalidate those recommendations, which are meant only as guidelines for the prevention of possible toxicity.

TD = Transdermal
SR = Sustained release
NP = None published
NR = Not recommended
ROB = Risk outweighs benefits

IM = Intramuscular
IV = Intravenous
PO = By mouth
SQ = Subcutaneous
q = Every

mg = Milligram
kg = Kilogram
hr = Hour

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transdermal methimazole to her hyperthyroid cat. Clients who are to administer compounded transdermal medications should be counseled about the proper application of the drug, including self-protection from the agent. The exact dose should be clearly listed on the syringe used for administration, and techniques used to put on and remove gloves without contaminating the skin should be taught. The use of finger cots is usually discouraged because they are very difficult to remove without contaminating the skin. Many compounding pharmacists dispense (in addition to the prescribed medication) transdermal kits containing instructions for the administration of the drug, protective gloves, and specific information about monitoring the patient that receives the transdermal therapy.

Regulatory Environment for Transdermal Compounding

Compounding transdermals is currently a complicated legal issue. Before 1996, all compounding for animals was technically illegal under the Animal Drug Amendment of 1968. As the FDA began to recognize the importance of compounding for animal patients, the Compliance Policy Guideline (CPG) for Compounding for Animal Patients (CPG 7125.40) was created in July 1993. This FDA-generated guideline did not legalize

compounding for animals but equipped regulatory inspectors with discretionary boundaries for enforcement. In 1996, the Animal Medicinal Drug Use Clarification Act (AMDUCA) codified compounding from approved products (human or veterinary) for nonfood animals. The AMDUCA, however, specifically excluded compounding from raw or bulk chemicals; as a result, that type of compounding remains illegal. Ideally, transdermals should be compounded from bulk chemicals to prevent the addition of impurities and to obviate problems from the binders and excipients in manufactured products. Thus compounding a safer transdermal medication from bulk chemicals juxtaposes law and good compounding practices.

The CPG for Compounding for Animal Patients guides the regulatory discretion of the FDA inspector. One of the areas of highest regulatory priority is whether human health suffers as a result of compounding. Transdermals may present a significant health risk to the caregiver because they must always be applied to an animal by a human. For that reason, the FDA is currently watching the transdermal arena very closely. At the time of this writing, the FDA is examining the CPG for Compounding for Animal Patients, with plans for revising in the near future. The FDA recommendations that will be published then are unknown. The American Veterinary Medical Association has also expressed great concern about the widespread use and misuse of compounded products (particularly transdermals), and has issued a position statement on compounding for animal patients. According to that statement, compounding should occur only within the veterinarian-client-patient relationship, should be performed within the guidelines of the AMDUCA, should not be performed for use in food animals, and should be limited to drugs demonstrated to be safe and effective in the target species. Unfortunately, there is little published evidence supporting or refuting the safety or efficacy of compounded transdermals in any species.

Current Evidence Supporting Transdermal Dosing

At time of publication, there are no randomized, controlled, double-blinded studies documenting the safety and efficacy of transdermal drugs used in animals. There are laboratory animal studies documenting *in vitro* penetration for many transdermally applied agents, but few *in vivo* studies. Some case reports on the human use of compounded transdermals are also present in the literature, but again there are no controlled studies and no pharmacokinetic studies. Veterinary newsletters² have published anecdotal accounts of the efficacy of compounded transdermals, but many of these anecdotal reports fail to include any definitive post-treatment laboratory data. They, unfortunately, do not present convincing evidence for efficacy of transdermals. There are two retrospective medical records reviews of transdermal methimazole used to treat cats with hyperthyroidism.^{3,4} These reports document efficacy with pre- and post-treatment T4 values after transdermal methimazole was applied. Between the two studies, 25 of 29 cats demonstrated a return to normal T4 levels and improvement

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in clinical signs after treatment with transdermal methimazole. Pharmacokinetic studies of transdermal drugs are also beginning to be published. The University of Wisconsin detected serum levels of methimazole in 2 of 6 cats following a single dose of methimazole compounded in PLO.⁵ Despite the inconsistent results of that study, the investigators believe that single dosing underestimates the bioavailability of transdermally administered drugs, and they are subsequently conducting a chronic dosing study in clinically hyperthyroid cats. North Carolina State University has just completed a kinetics study for intravenous and transdermal diltiazem, which showed very promising results in terms of systemic availability of compounded transdermal diltiazem.⁶ Blood levels of diltiazem were detected in all cats studied (4) after a single dose of transdermal diltiazem compounded in Lipoderm, a proprietary biphasic percutaneous absorption-enhancing gel that is not temperature sensitive. Another recently published study looked at the systemic absorption of lidocaine following topical application of lidocaine in a liposome-encapsulated cream.⁷ This study demonstrated that there was minimal systemic absorption of lidocaine from this base after topical administration. It is important to note, however, that the preparation studied, Emla-Max, is *not* intended for systemic absorption but only penetration into the epidermis to allow local anesthesia to facilitate invasive procedures. While this study has been cited by some as evidence that transdermal drugs are not available for systemic delivery, it was conducted to prove that lidocaine was not significantly transdermally absorbed, as this would negate the utility of this topical dosage form. Texas A&M's Veterinary Clinical Pharmacology Laboratory (www.cvm.tamu.edu/vcpl/Research/Transdermal/transderm_main.htm) has also been funded by the Morris Animal Foundation to study 12 different compounded transdermals. To date its studies have been limited to dogs, and results have not yet been published. Until further scientific evidence is published, however, compounded transdermal dosage forms should be used with extreme caution and only after traditional administration routes have been exhausted.

Collecting Clinical Evidence of Safety and Efficacy

A pharmacist who receives a prescription for a compounded transdermal medication should enter a partnership with the prescribing veterinarian and client to collect prospective data on the results of therapy. The pharmacist should attempt to collect the basic elements of the prescription and all relevant patient demographic information (patient name, weight, diagnosis, species, gender status, drug history, diagnostic laboratory values, and the date of the next scheduled follow-up visit with the veterinarian). Within 48 hours of having dispensed the transdermal medication, the pharmacist should phone the client and note the exact date and time of the administration of therapy. The client's comments (impressions of therapy, possible adverse effects) should be noted. As soon as the client has completed the follow-up visit to the veterinarian, the

pharmacist should ask the veterinarian about the results of posttreatment diagnostic tests. All values and comments should be noted in a readily retrievable format.

Summary

The use of compounded transdermal medications is a milestone in veterinary drug therapy. Compounded transdermal medications can be life-saving therapeutic agents for cats that cannot tolerate the administration of traditional dosage forms. Unfortunately, scientific evidence of compounded transdermals is currently lacking. Until such studies have been conducted and are readily accessible, pharmacists and veterinarians must collaborate to decide when compounded transdermal therapy is appropriate, safe, and effective. By analyzing the pharmacokinetic parameters of the drug and identifying objective assessment parameters for efficacy and toxicity, the pharmacist and veterinarian can attempt to predict the behavior of a transdermally applied medication in a given patient. Careful monitoring, communication, and documentation will increase the success of any transdermally administered therapy. Regardless of the likelihood of clinical success from using a compounded transdermal medication, the safety of the caregiver must be the highest priority.

References

1. US Food and Drug Administration. FDA concept paper: Drug products that present demonstrable difficulties for compounding because of reasons of safety or effectiveness, Rockville, MD: Food and Drug Administration. Available at: http://www.fda.gov/cder/fdama/difconc.htm#P146_41537, Accessed April 1, 2002.
2. Ahl, H. Insulin in PLO for dogs with newly diagnosed diabetes mellitus. *RxTriad* 2000; Winter:1.
3. Wingate, G. Transdermal methimazole in the treatment of 16 cats with hyperthyroidism. *IJPC* 2002;6(5):344-345.
4. Hoffman G, Marks S, Taboada J, et al. Topical methimazole treatment of cats with hyperthyroidism. *J Vet Intern Med* 2001, 15:299.
5. Hoffman S, Yoder A, Trepanier L. Bioavailability of transdermal methimazole in a pluronic lecithin organogel (PLO) in healthy cats. *J Vet Pharmacol Ther* 2002;25:189-193.
6. Nolan T, Davidson GS, DeFrancesco T. Pharmacokinetics of intravenous and transdermal diltiazem in healthy cats. Paper presented at: Annual Research Forum, North Carolina State University, College of Veterinary Medicine, Raleigh, North Carolina, March 8, 2002.
7. Fransson B, Peck K, Smith J et al. Transdermal absorption of a liposome-encapsulated formulation of lidocaine following topical administration in cats. *Am J Vet Research* 2002;63(9):1309-1312.
8. Mitchener KL, Oglivie G, Wash AM, et al. Pharmacokinetics of oral, subcutaneous, and transdermal metoclopramide in client-owned dogs: A randomized study. In *The Proceedings of the 21st Annual Meeting of the Veterinary Cancer Society, Baton Rouge, Louisiana, 2001*. Published by the Veterinary Cancer Society, P.O. Box 1763, Spring Valley, CA 91979.

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